

## Clinical use of second-generation antipsychotics in children

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### Abstract

**Background:** The use of second-generation antipsychotic (SGA) medication among child and adolescent psychiatric patients has increased worldwide in recent years. The increase appears to have been more extensive in the USA than in European countries, but the tendency is similar. However, after a peak the use seems to have declined in the USA. Simultaneously with the increasing numbers, the duration of SGA use has lengthened, indications have broadened, and off-label use has increased. Despite existing follow-up recommendations and evidence for the metabolic adverse effects of SGAs in children, research evidence has not translated into clinical practice.

**Objective:** The aim of this study was to assess the clinical use and follow-up practices of SGA medication among child psychiatric patients of one university hospital in Finland.

**Method:** This retrospective patient report-based study was conducted at the Child Psychiatric Clinic of Tampere University Hospital, Finland. The study sample consisted of 133 patients who were younger than 13 years when initiating SGA treatment and had an ongoing SGA medication during the study period. The study sample was divided into two groups according to diagnosis to examine whether there were differences between patients with an autistic or a developmental disorder (F83-84) and patients with other psychiatric diagnoses.

**Results:** This study showed that SGA use in children younger than 13 years was mainly off-label. Irrespective of diagnosis, the most common indication was aggression. Especially children with psychiatric diagnoses other than developmental disorders had multiple socio-demographic risk factors and adverse life experiences in their background. The follow-up practices were diverse and partly irregular.

**Conclusions:** A need for systematic SGA monitoring practices and dialogue between the medical specialties treating children and their families is evident.

**Keywords:** antipsychotic medication; second-generation antipsychotic; children; follow-up practices; adverse life events

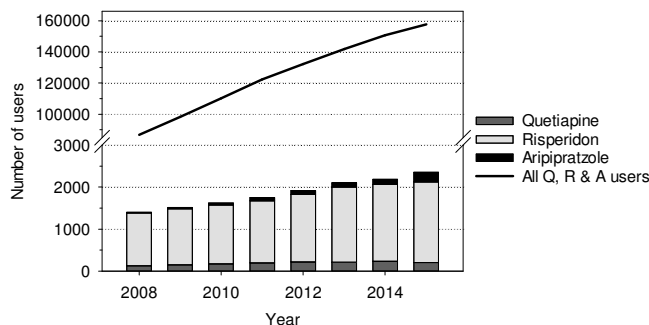
### Introduction

The use of second-generation antipsychotic (SGA) medication among child and adolescent psychiatric patients has increased worldwide in recent years (1-5). The increase appears to have been more extensive in the USA than in European countries, but the tendency is the same (3,6). However, after a peak, SGA use seems to have declined in the USA (7,8). At the same time, the duration of SGA use in children has lengthened, indications have broadened, and off-label use has increased (3,9,10). The use of SGAs in

children and adolescents seems to be increasing from the age of 7 to 8 years onwards, predominantly in male patients (2-5).

In Finland, the prevalence of antipsychotic use among children and adolescents under the age of 18 years has increased from 4.3 to 6.7/1000 between 2008 and 2015 (5). Simultaneously, the proportion of children and adolescents in this age group using antipsychotic medication and having a diagnosis of a psychotic disorder or psychotic symptoms decreased from 19% to 11% (5). According to the statistics of

the Social Insurance Institution of Finland, during the same period, prevalence of use among children younger than 13 years increased from 1.7 to 2.8/1000. The three most commonly used SGAs in this age group were risperidone, aripiprazole, and quetiapine. The number of children younger than 13 years using these drugs in Finland has steadily increased in recent years, and the increase is most apparent for aripiprazole (14-fold) and risperidone (1.5-fold). However, the proportion of children younger than 13 years among all SGA users in Finland has remained quite steady (1.4% to 1.6%) as the number of all users has also increased (Figure 1). According to a recent Finnish study, SGAs were the most common medication among child psychiatric urgent-care in-patients at Kuopio University Hospital, and the use was mostly off-label (11).



**FIGURE 1.** Second-generation antipsychotic use of 0 to 12-year-old children and all users in Finland (2008 to 2015)

The official criteria for SGA use by children younger than 13 years vary to some extent among countries. In the USA, the Food and Drug Administration (FDA) approves aripiprazole, quetiapine, and risperidone for the treatment of bipolar disorder among children older than 10 years (12). Aripiprazole and risperidone are also approved for the treatment of irritability associated with autism (12). In Finland, only risperidone and ziprasidone are approved for children younger than 13 years. Ziprasidone is approved for manic episodes of bipolar disease in children older than 10 years and risperidone for short-term use ( $\leq 6$  weeks) in the treatment of conduct problems in children older than five years with developmental disorders or mental retardation. As official indications for SGA use are scarce, use among children is mostly off-label (2).

Children and adolescents with autism spectrum disorders and intellectual disability represent an increasing population treated with SGAs (13). SGA

use is also common among children with attention deficit hyperactivity disorder or disruptive behaviour disorders (2,3). SGA medication is also used for children and adolescents with various other diagnoses – such as psychosis, mood and tic disorders, and obsessive compulsive disorder – and in symptomatic treatment for aggressive behaviour despite the primary diagnosis (1,2,8,10,14).

When looking at the socio-demographic background factors of paediatric patients using SGAs in the USA, studies show that the increase in SGA use has occurred disproportionately more often among publicly than privately insured patients (1,7). Those in foster care seem to be especially prone to antipsychotic prescriptions among publicly insured children (7). Children in foster care have often experienced traumatic life events, which are, among other individual and environmental factors, known risk factors for several mental health disturbances (15-17). These kinds of experiences are probably more common in children and adolescents treated by psychiatric services than in the general population. For example, adverse life events were frequent among adolescent-aged psychiatric in-patients suffering from bipolar disorder type I (58%) and catatonia (57%) (18). In a study by Ford et al. (19), in a clinical sample of child psychiatry out-patients aged four to 18 years, one in three participants had a history of exposure to interpersonal violence.

There is some evidence of the benefits of SGA use in children. SGAs, particularly risperidone and aripiprazole, have shown to be efficient in the treatment of irritability, aggression, self-injury, and possibly stereotypic behaviour in autism (20-24). SGAs also appear to reduce challenging behaviour in the short term among children with intellectual disabilities (25). There is some evidence that risperidone has an effect on disruptive and aggressive behaviour in the short term even among children and adolescents with a normal IQ (26,27). Risperidone and aripiprazole appear to be promising for treating tic symptoms in children with Tourette syndrome (28,29). With psychosis or schizophrenia, the efficacy of SGAs appears to be similar in children, adolescents, and young adults (30-32). Aripiprazole also appears to be effective in paediatric bipolar disease (30,33). However, the available studies mostly cover only the short-term use of SGAs, which seldom fits the clinical reality.

In children, the therapeutic profile and adverse effects of SGAs seem to differ from those in adults, and children also appear to be more vulnerable than adults to some SGA-induced adverse effects (34). Sedation, hyperprolactinemia, and metabolic disturbances, such as weight gain, dyslipidaemia, and hyperglycaemia, are known SGA adverse effects that

can have far-reaching consequences through metabolic, endocrinological, cardiovascular, and psychological effects (34-38). We also know very little about the long-term effects of SGAs on the developing central nervous system.

The detected increase in SGA use has induced attempts to monitor and improve SGA prescription practices around the world (7,39,40). All monitoring recommendations emphasize on the appropriate use of psychosocial interventions and the regular monitoring of metabolic and other adverse effects (41). The guidelines of the American Academy of Child and Adolescent Psychiatry (AACAP), the

Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA), and the National Institute for Health and Care Excellence (NICE) in the UK include recommendations for monitoring and managing the adverse effects of SGA in children (Table 1) (39,40,42). In Finland, there are national clinical guidelines for the treatment of schizophrenia in adults, but not for children. Psychotropic medications are however, recommended to be initiated for children in specialist-level health care services (5), with the exception of attention deficit hyperactivity disorder medication (methylphenidate).

**TABLE 1.** Recommendations for monitoring second-generation antipsychotic treatment according to National Institute for Health and Care Excellence (NICE), American Academy of Child and Adolescent Psychiatry (AACAP), and Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) (39,40,42)

Issued by	Baseline	Follow-ups			
		1	2	3	4
NICE		Weekly (first 6 weeks)	12 weeks	Every 6 months	
	Growth chart*, WHC, RR, pulse, fb-gluc, HbA <sub>1c</sub> , lipids, prolactin, MD, nutritional status, diet, physical activity	Growth chart, MD, efficacy, side-effects	Growth chart, MD, RR, pulse, fb-gluc, HbA <sub>1c</sub> , lipids, prolactin, physical health, efficacy, side effects	Growth chart, MD, WHC, RR, pulse, fb-gluc, HbA <sub>1c</sub> , lipids, prolactin, physical health, efficacy, side effects	–
AACAP		Regular intervals			
	Family history, BMI, WC, RR, pulse, fb-gluc, lipids, MD	BMI, RR, pulse, fb-gluc (HbA <sub>1c</sub> if needed), lipids <sup>†</sup> , MD	–	–	–
CAMESA		1, 2, 9 months	3 months	6 months	1 year
	Growth chart, BMI, WC, RR, NEU, fb-gluc, insulin, lipids, ASAT, ALAT, TSH (with quetiapine), prolactin	Growth chart, BMI, WC, RR, NEU	Growth chart, BMI, WC, RR, NEU, fb-gluc, insulin, lipids, prolactin	Growth chart, BMI, WC, RR, NEU, fb-gluc, insulin, lipids, ASAT, ALAT, TSH (with quetiapine)	Same as baseline

Note. ECG recommendations are not included

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; fb-gluc, fasting glucose; HbA<sub>1c</sub>, glycosylated hemoglobin; lipids, blood lipid profile; MD, movement disorders; NEU, neurological examination; TSH, thyroid-stimulating hormone; RR, blood pressure; WC, waist circumference; WHC, waist and hip circumference

\*Includes weight and height

<sup>†</sup>If significant weight changes and/or a family history indicating risk

Recommendations and follow-up protocols seem to be helpful in clinical work and appear to increase monitoring and possibly have an effect on prescribing practices (7,43,44). Despite the already existing recommendations, there has been a lag in the translation of research evidence into clinical practice (39,45). Rates of metabolic monitoring of SGA have been low according to several studies. Rodday et al. (46) found that 66% of psychiatrists reported routinely asking about the patient's medical history, 92% reported monitoring the patient's growth, 81% reported monitoring the patient's plasma glucose and lipids, 23% reported measuring the patient's waist circumference, and 12% reported monitoring the patient's ECG. Being able to measure vital signs, height, and weight on site was associated with a higher probability of monitoring height and weight (46). In an audit performed in the UK, Pasha et al. (44) discovered that for in-patients at a child and adolescent mental health unit, the parameters measured most often before SGA initiation included BMI and hip-to-waist circumference; however, the monitoring rate of these measurements was only 60%. In the USA, many monitoring initiatives have taken place in the foster care system, and as a result, SGA-treated children in foster care are now more likely than other publically insured children to receive metabolic monitoring, and, in addition, psychosocial interventions (7). Nevertheless, both glucose and lipid monitoring failed in 72% of these foster children and in 82% of others (7).

Some children appear to be more vulnerable than others in developing metabolic adverse effects, and an important goal of an SGA monitoring procedure should be to identify as early as possible those children who are at particular risk for adverse effects (36,47). Some specific genes have already been linked with the increased risk of adverse effects with SGAs, but there are no gene tests available yet in everyday clinical work (47,48). In the light of current evidence, screening and monitoring practices should thus be emphasized.

### **Aims of the study**

The aim of this study was to assess the clinical use, indications, and follow-up practices of SGA medication among child psychiatric patients at Tampere University Hospital (TAUH), Finland. This study also aims to describe the medical and socio-demographic background factors of SGA-treated children as well as the possible benefits and adverse effects of SGA medication.

### **Method**

This study was conducted at the Child Psychiatric Clinic of TAUH and was based on patient reports.

With a catchment area of approximately half a million people, TAUH is one of five university hospitals in Finland offering specialist-level health care services. The Child Psychiatric Clinic gives in-patient and out-patient services for children aged 0 to 12 years. Children aged 13 to 18 years are taken care of in adolescent psychiatry, which in Finland is a separate speciality. Children with a diagnosis of mental retardation are referred to separate services. Children are referred to TAUH by the health care centres and community hospitals of the district. Guidelines are available for the referral practices to specialist-level child psychiatric services. During the study period (1 October 2013 to 1 October 2014), 1633 children were treated at the clinic.

The inclusion criteria for the study were that the patient was younger than 13 years when initiating SGA treatment, that the medication was initiated at the TAUH clinic, and that the SGA medication was ongoing during the study period. These criteria were met by 133 patients, whose patient reports were examined until the date the medication was discontinued, the patient was referred to another clinic, or until 31 May 2015, whichever came first.

The first author (K.K.) collected information from the patient reports and recorded them. Selected patient reports were reviewed by the second author (L.P.), who also offered second opinion on request from the first author. The data collected from patient reports consisted of the patient's age, the conclusion of the cognitive evaluation, and other socio-demographic and medical factors at the SGA initiation phase. The conclusions of cognitive evaluations were dichotomized as intelligence within normal variation or below, based on patient report markings of either the attending physician or a psychologist. Information on SGA medication use (generic name, duration, reasons for discontinuing or changing medication) and other psychotropic medications as well as information on the patient's diagnoses and indications (or main symptoms) attached to the SGA initiation were collected or deduced from the patient reports. The reasons for discontinuation or changing the SGA were categorized for analyses by the first author as: adverse effect, no benefits, adverse effects more significant than possible benefits (unfavourable risk-benefit ratio), symptoms diminished so that the medication was no longer needed, and no information. In addition, information on the psychiatric and other medical history of the patient and his/her family was recorded. The possible benefits and adverse effects of SGA medication were extracted from the physicians' evaluations recorded in the patient reports. The available information of possible benefits was classified as: considerable

benefit, some benefit, uncertain, no benefit, and no information. The adverse effects, such as weight gain, and neurological, endocrinological (e.g., gynecomastia, menstruation disturbances), and other mentioned effects were recorded separately. Information concerning the follow-up protocols, such as medical evaluations made during the follow-up period (physical status, weight, and height) and possible consultations made by child psychiatrists to other medical specialties (e.g., cardiology or paediatrics) were recorded. The patient's age-adjusted BMI score was calculated at the analysis phase from the existing weight and height data (if both measurements were available from the same time point) using the tables of the new Finnish growth references (49).

To examine whether there were any differences between patients having an autism spectrum or developmental disorder diagnosis and patients with other psychiatric diagnoses, the study sample was divided into two groups based on diagnosis using the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10)* (50). The first group (the PDD/DD group) consisted of 40 (30%) children with a pervasive developmental disorder (F84) diagnosis and seven (5%) patients with a diagnosis of mixed specific developmental disorders (F83). The second group (the non-PDD/DD group) consisted of 86 (65%) patients with various other diagnoses. Results for the groups where there are statistically significant differences are reported separately; otherwise, the results are reported for the entire sample.

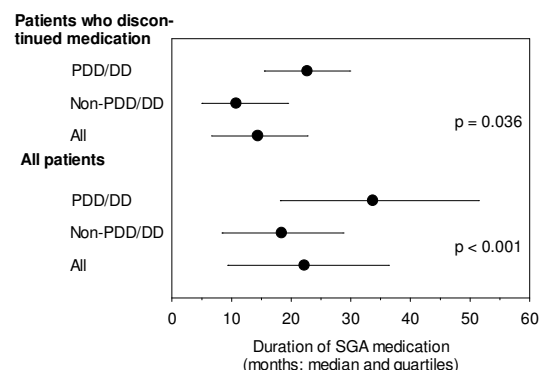
The results of categorized variables are reported as frequencies (percentages or number of cases, as appropriate). For normally distributed continuous variables, means (M) and standard deviations (SD) are given, and for other continuous variables, medians and quartiles (Md, Q<sub>1</sub>, Q<sub>3</sub>) are reported. For testing the significance of differences between the PDD/DD and non-PDD/DD group, Pearson's chi-squared test, Fisher's exact test, or the Mann-Whitney U-test were used, as appropriate. A *p*-value of less than 0.05 is considered significant, and a value between 0.05 and 0.10 is considered indicative; values up to 0.10 are reported. SPSS v.23 was used for all statistical analyses.

## Results

Eighty-one percent of the study sample were boys. The mean age at the time of SGA initiation was 9.3 years (SD, 2.1 years). In the PDD/DD group, the children were younger at the time of SGA initiation than the children in the non-PDD/DD group (M 8.6 years, SD, 2.0; and M, 9.7 years, SD, 2.0, respectively; *p* = .002). The age distribution of the patients showed

two peaks, one during the early years of school (6 to 8 years) and the second at pre-puberty (11 to 12 years). Cognitive evaluation was performed for 85% of the children, and a conclusion about intelligence status was available for all but three of them. Eighty-one percent of those evaluated had an intelligence profile within normal age variation. One patient had a diagnosis of mental retardation. Information on whether the cognitive evaluation was performed or not was lacking in four patient reports. Cognitive evaluation was performed more frequently in the PDD/DD group than in the non-PDD/DD group (96% vs. 78%, *p* = .010), but there were no statistically significant differences between groups in the results of the evaluations. Seventy-nine percent of the study patients had been treated at least once in their lifetime at a psychiatric in-patient ward.

The most common SGA drug at initiation was risperidone (93%). Quetiapine (6%) and aripiprazole (2%) were less common. Risperidone was indicatively more common than other SGAs in the PDD/DD group than in the non-PDD/DD group (98% vs. 90%, *p* = .097). Sixteen percent of the patients had their medication switched to another SGA once, 6% twice, and two patients three times. The most common reasons for switching the SGA were adverse effects (52%) and an unfavourable risk-benefit ratio – that is, the attending physician had judged that adverse effects were more significant than possible benefits (48%). Thirty-two percent of the patients who had their SGA switched had no benefits from the initiation drug. In the PDD/DD group, there were fewer alterations in SGA medications than in the non-PDD/DD group (17% vs. 34%, *p* = .035), and the reason for switching was less frequently an adverse effect (31% vs. 73%, *p* = .032).



**FIGURE 2.** Duration of second-generation antipsychotic (SGA) medication. Figures in the "all patients" group do not describe the genuine duration of SGA medication because the duration after the endpoint of the follow-up is not known



Figure 2 shows the duration of SGA medication in this study. Almost one-fifth of the patients discontinued medication completely during the study period. The median duration of SGA medication among these patients was 14.4 months. In the PDD/DD group, the duration of SGA treatment was longer than in the non-PDD/DD group (Md, 22.7 vs. 10.8 months,  $p = .036$ ). The most common reasons for discontinuation were that the patient's symptoms had diminished to a level where

medication was no longer needed (52%) or that the risk-benefit ratio was considered unfavourable (30%). When taking all study patients into account, the median duration of SGA medication by the end of the study period was 22.2 months. In the PDD/DD group, the duration was longer than in non-PDD/DD group (Md, 33.7 vs. 18.4,  $p < .001$ ). However, this figure does not describe the actual duration of SGA medication in this group because the duration after the end of follow-up is not known.

**TABLE 2.** International Statistical Classification of Diseases and Related Health Problems, 10th Revision, diagnoses of second-generation antipsychotic (SGA)-treated children (n=133)

Diagnoses	ICD-10 class	%
Hyperkinetic disorders	F90	50
Conduct/mixed conduct and emotional disorder	F91-92	40
Pervasive developmental disorders	F84	30
Obsessive compulsive disorder	F42	13
Disorders of social functioning with onset specific to childhood and adolescence*	F94	13
Reaction to severe stress/adjustment disorders	F43	10
Tic disorders	F95	8
Emotional disorder with onset specific to childhood	F93	7
Disorders of psychological development	F80-82	7
Depressive episode	F32	6
Bipolar affective disorder	F31	5
Psychotic disorders	F23, F29	5
Mixed specific developmental disorders	F83	5
Other mood (affective) disorders	F38	5
Phobic and other anxiety disorders	F40-41	3
Dissociative (conversion) disorders	F44	3
Other behavioural and emotional disorders with onset usually occurring in childhood and adolescence†	F98	2
Eating disorders	F50	1
Unspecified mental retardation	F79	1

Note. Each child could have more than one diagnosis

ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision

\*Reactive attachment disorder F94.1 (n=5), other childhood disorders of social functioning F94.8 (n=12)

†Non-organic enuresis F98.0 (n=1), non-organic encopresis F98.1 (n=1)

Polypharmacy was common among the patients in the study. Nine patients were simultaneously using another antipsychotic medication, most commonly (five patients) levomepromazine. The actual rate of simultaneous use of two different antipsychotic agents was higher due to cross-titration periods when switching from one medication to another. Sixty-eight percent of the study patients had undergone at least a short-term treatment trial with some other psychotropic medication (not including melatonin) in addition to SGA during their treatment at the Child Psychiatric Clinic. Fifty-three percent had used one medication other than SGA and 14% two or three. The use of methylphenidate was more common in the PDD/DD group than in the non-PDD/DD group (79% vs. 58%,  $p = .022$ ). Twenty-five percent had had at least a trial with atomoxetine and 16% with selective serotonin reuptake inhibitors. Fourteen percent of the study patients had had

benzodiazepines as requisite medication at some point of their treatment. Almost two-thirds (63%) of the patients had undergone at least a short-term melatonin treatment for sleep problems.

All of the study children had at least one ICD-10 F-category psychiatric diagnosis (50) at the time of SGA initiation and 75% had at least two F diagnoses, the maximum being four (Table 2). Children in the PDD/DD group had more often comorbid disorders, 55% of them having two F category diagnoses and 38% having three or four, while the respective numbers in the non-PDD/DD group were 47% and 19% ( $p = .001$ ). The most common diagnoses in the non-PDD/DD group were F91-92 (conduct/mixed conduct and emotional disorder; 49%,  $n = 42$ ) and F90 (hyperkinetic disorders; 44%,  $n = 38$ ). F91-92 and F31 (bipolar affective disorder) diagnoses were more common in the non-PDD/DD group than in the PDD/DD group (49% vs. 23%,  $p$

= .005, and 8% vs. none,  $p = .051$ , respectively). Thirty-nine percent of the patients had also at least one ICD-10 Z diagnosis (factors influencing health status and contact with health services), implying multiple environmental factors influencing the patient's mental well-being.

The indication for SGA initiation was clearly stated in 61% of patient reports. In general, indications and symptoms were diverse, and 92% of the patients had two or more indications or main symptoms. The most common indications or core/main symptoms for SGA initiation were aggression (in 75% of the patients) and behaviour problems (74%) independent of diagnosis. Mood swings were a more common indication in the non-PDD/DD group (24% vs. 9%,  $p = .035$ ) and sleep problems as indication indicatively associated with the PDD/DD

group (17% vs. 6%,  $p = .063$ ). The officially approved criteria for SGA medication (here risperidone, which was the most commonly used SGA in this study) use in Finland is short-term treatment of conduct problems of children older than 5 years with developmental disorders or mental retardation. None of the SGA-medicated children in this study fulfilled all these criteria. With loose interpretation, the 47 (35%) patients in the PDD/DD group fulfilled the official criterion for diagnosis of developmental disorders or mental retardation. Forty-five of these patients also fulfilled the criterion for age (> 5 years) and 34 fulfilled the indication criterion of aggression/aggressive behaviour, but in none of the study patients was the medication short-term.

**TABLE 3.** Family background of the second-generation antipsychotic-treated children

	All (%)	PDD/DD (%)	Non-PDD/DD (%)	<i>p</i>
<b>Family status (n=133)</b>				<.001
Biological parents	37	57	26	
Parental separation	40	36	42	
Foster home	18	6	24	
Other (e.g. adoption)	5	0	8	
<b>Number of siblings (n=126)</b>				NS
None	21	23	20	
One	38	40	37	
Two or more	41	36	43	
<b>Mother's working status (n=133)</b>				.018
Working at least part time	53	68	45	
Other or not known	47	32	55	
<b>Father's working status (n=133)</b>				NS
Working at least part time	57	64	54	
Other or not known	43	36	47	
<b>Alcohol/drugs (n=83)</b>	60	44	71	.021
<b>Psychiatric history of first-degree relatives</b>				
Schizophrenia, bipolar disease or other psychosis (n=67)	33	15	45	.016
Depression (n=88)	67	61	72	NS
Suicide (n=133)				NS
Committed	2	2	2	
At least one attempt	7	2	9	
<b>Child exposed to violence (n=133)</b>	41	30	48	.065
Exposed to domestic violence	11	4	15	
Been object of physical punishment or other domestic violence	12	13	12	
Both exposed and been object	11	6	13	
Other kind of violence exposure (e.g. war experiences)	8	6	8	

*Note.* In variables concerning suicide and exposure to violence, missing information was categorized as "no". In all other variables missing information was separated. Therefore, the total number of cases vary by variable

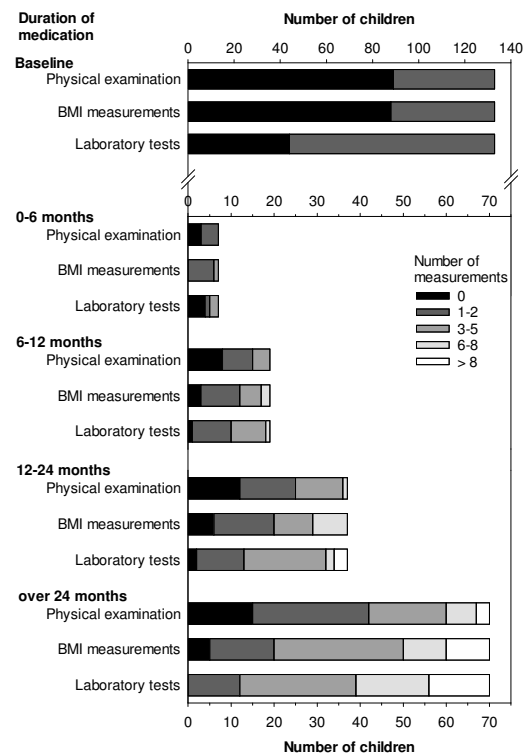
The study patients had diverse social stress factors and adverse life events in their past (Table 3). Less than 40% of the patients had both biological parents as caregivers at the time of SGA initiation. Parental separation was common (40%), and 18% of the patients were in foster care. There was parental substance abuse in more than half of the families. A family history of psychiatric disorders was recorded for 84% of the patients (whereas a family history of somatic diseases was recorded for 53% of the patients). There was a first-degree family member who had a diagnosis of schizophrenia, bipolar disease, or other psychosis in one-third of the families. Over a half of the patients had a depressed family member and about one-tenth had a family member who had attempted or committed suicide. Exposure to some kind of violence was mentioned in 41% of the patient reports.

The everyday functioning of the patient's parents in the PDD/DD group appeared to be better than that in the non-PDD/DD group. About half of the mothers and fathers of the study patients were working at least part time. However, the employment of mothers was statistically significantly more common in the PDD/DD group than in the non-PDD/DD group, and children in the PDD/DD group also had both biological parents as caregivers more often. In the PDD/DD group, out-of-home placements were rarer than in the non-PDD group, and there was significantly less parental substance abuse and fewer first-degree relatives with bipolar or other psychoses. Exposure to violence was also indicatively less common in the PDD/DD group than in the non-PDD/DD group (see Table 3).

In 36% of the patient reports, there was no information on growth history at the time of SGA initiation. When reported, growth history was normal in 68% of the patients, while there was some deviance (e.g., overweight, slow growth) in the remainder prior to SGA initiation. Six patients were reported to have been drinking alcohol and five patients were reported to be smoking. One of the patients had voluntarily told the physician about experimental substance use. In general, information on the patient's possible substance use was missing.

In 81% of the cases, the attending physician reported either considerable or at least some benefit due to the SGA medication. Three percent had no benefits from the SGA medication. In 16% of the cases, the possible benefits remained uncertain or the information was lacking. In many cases, there was also fluctuation in symptoms despite the medication. In 28% of the cases, the attending physician reported no adverse effects. One adverse effect was reported in 32% of the patients and 40% had two or more adverse effects. The most frequent adverse effects

were increased appetite and weight gain, which were reported in 36% and 35% of the cases, respectively. Somnolence, usually in the SGA initiation phase, was reported in 33% of cases and other neurological adverse effects in 10% of the patient reports. All other reported adverse effects (increased irritation, mammillary gland symptoms, disturbances in menstrual cycle, urinary symptoms, headaches, nosebleeds, abdominal pain or swelling, and loss of appetite) were each mentioned at most in 7% of the patient reports.



**FIGURE 3.** Physical examination, BMI measurements, and laboratory tests performed during the second-generation antipsychotic treatment

Figure 3 shows a summary of the frequency of physical examination, laboratory tests, and BMI measurements performed during the study period. At SGA initiation (baseline), some kind of physical examination other than measurement of height or weight was performed on 33% of the patients. Almost the same proportion of the patients (29%) had no physical examination during follow-up. Approximately one-fifth of the patients in the longest treatment category (over 24 months) had no physical examinations during follow-up. At baseline, 38% of the patients had their weight measured and 34% had their height measured. Twenty percent had



their height measured once and 69% had their height measured twice or more often during the follow-up. Weight was measured once in 16% of the patients, and 77% had at least two weight measurements during the follow-up. Ten (8%) patients had no information on weight and fourteen (11%) patients had no information on height during the follow-up. In some reports, it was mentioned that growth was followed elsewhere, but the information did not always reach the attending physician. Baseline laboratory tests were more frequent than physical examination. At baseline, some laboratory tests were performed for 67% of the patients and plasma lipids and glucose, as indicators of metabolic condition, were checked for 55% and 61% of the patients, respectively.

Twenty-five percent of the patients had one and 10% two or three consultations with a paediatric cardiologist during the study period. A consultation was most often performed as a paper consultation. Indications for consultations were diverse, but mostly involved the interpretation of an ECG if the psychiatrist considered it aberrant. The cardiologist did not find absolute obstacles for SGA use in any of the consultations. However, in two patients, cardiological adverse effects (prolonged QT interval) were mentioned as a reason for discontinuing or switching the SGA. Other paediatricians (e.g., neurologist or endocrinologist) were consulted at least once for 32% of the patients. Nine patients were referred to a nutritionist for dietary advice.

## Discussion

In this study we assessed the clinical use of SGAs in 133 child psychiatric patients aged 12 years or younger. Children in the study had multiple diagnoses, and polypharmacy was common. Most (79%) of the patients had had in-patient treatment, reflecting their symptom severity and poor functional capacity. Comorbidity was common, with 75% of all children receiving more than one psychiatric diagnosis. Independently of the diagnoses, the main SGA target symptom was aggression; however, the indication was clearly stated in only 61% of the patient reports. The official indications for SGA medication for children younger than 13 years are few. Nevertheless, these medications are frequently used for varying indications in this age group (1,2,8,10,14). In this study, the data were collected from a geographically restricted area in Finland. However, the findings are in line with previous studies (2,10,11). SGA use was mostly off-label, since none of the patients fulfilled all of the official indication criteria.

Various studies show that the significant risk for metabolic and other SGA-induced adverse effects

calls for appropriate monitoring (34-38). However, the content and schedule of the physical evaluations and follow-up practices of SGA medications have been diverse in child psychiatric clinical work (7,39,44-46), as was also observed in this study. Only about one-third of the study patients had undergone a physical evaluation at SGA initiation. Approximately one-fifth of the patients medicated for over 24 months had no physical examination at any of the follow-up visits. Furthermore, information on growth history was lacking of about one-third of the patients. It is also noteworthy that information on the child's family history of somatic diseases, which is of importance when assessing risk factors associated with, for example, metabolic disorders, was often incomplete and less thoroughly documented than the family history of psychiatric illnesses.

Evaluating the benefits and risks of SGA medication among children is complex. SGA treatment for children is often associated with the symptomatic treatment of developmental or other disorders with a long duration (1,2,8,14,21,22,25). The average duration of the SGA medication was long in this study as well: the median duration was almost two years. Most of the SGA-treated patients (81%) in this study had an improvement in their symptoms at least to some extent, but symptom control seemed at times insufficient. In many cases, there was fluctuation in the symptoms despite the continuous medication and the possible benefits gained at the beginning did not remain so evident in the long run. During the early years, biopsychosocial development is rapid, and many aspects affect the possible symptom development. The two peaks in the SGA initiation age observed in this study – the first school years and pre-puberty – may both reflect times of increasing environmental and social demands for the child, and these times are also challenging from a family perspective. The many other psychotropic medication trials observed in this study may also have influenced symptom improvement or deterioration. In 16% of the patients in this study, the effect of the medication remained unclear. Despite this, the medication was often continued. The use of systematic assessment methods for examining changes in patients' functioning or response to medication was not possible in this study due to the source of information being patient records, which are often incomplete and somewhat unsystematic. Further studies on the subject are needed, and systematic assessment of functional capacity at the baseline and during follow-up should be encouraged.

In this study, the majority of children medicated with antipsychotics had remarkable adverse life

events in their background. Parental psychopathology and substance use, exposure to violence, and major changes in the family environment were common, and one in every five patients was in foster care. There were, however, differences in the background factors of the two patient groups: children in the non-PDD/DD group had more social stress factors than the children in the PDD/DD group. Adverse life events are, among other individual and environmental factors, known risk factors for mental disturbances in childhood and during the whole lifetime (15-17), and emotional dysregulation is found to be more common in children exposed to repeated or multiple traumas (15,16). While psychotropic medication can diminish behavioural and emotional symptoms and function as an important aid to improve the child's functional capacity, it is apparent that psychosocial support is necessary alongside medication. If the treatment plan is sufficiently integrated, medication can be a helpful aid in learning new skills of behavioural and emotional control, and, at best, can function as a catalyst for development. However, the sufficiency of psychosocial support for children treated with SGAs is a cause for concern. In a study by Olfson et al. (8), less than one quarter of SGA-treated patients aged 1 to 13 years received psychotherapy. In a study by Crystal et al. (7) more than one-third of children in foster care receiving SGA medication failed to receive psychosocial mental health services. However, as a result of several initiatives to improve the monitoring of SGA treatments in foster care children in USA, these children now appear to receive not only more adequate metabolic monitoring, but also psychosocial mental health services at rates higher than children in the general Medicaid population (7). This encouraging finding further highlights the importance of proper monitoring practices in clinical work. In this study we did not assess the psychosocial treatment measures separately. In specialist level child psychiatric services in Finland psychoeducation and therapeutic family counselling are, however, an integral element and need for other therapeutic interventions is evaluated individually for every patient. As psychosocial support is often put into practice in homes and schools by social or educational services, multi-professional co-operation is essential. Further studies of the subject in SGA treated children are needed.

Continuous dialogue between professionals and further education concerning medications and follow-up practices is important in child psychiatric clinical work. According to recent studies, psychiatrists' attitudes towards SGAs and performing physical examinations affect their

prescribing and monitoring practices (46,51). In addition, proper facilities and access to equipment for physical evaluation are of importance (46). Despite the already existing guidelines (39-42), there is still a need to standardize practices concerning antipsychotic medication use in psychiatric health care units treating children. When treating children with medications of long duration that affect both physical and mental development, liaisons should be encouraged between child psychiatry and paediatric medicine and child and adult psychiatry.

### **Clinical significance**

Results of this study are important for future planning of the child psychiatric health care in Finland. Children suffering from severe psychiatric problems need the most efficient treatment, including SGA medication when appropriate. The need and use of medication should in all circumstances be assessed and reported systematically, targeting initiation, response, and adverse effects. To improve practice standardization, we should further develop easy-to-use follow-up protocols that are child and family oriented. When treating children with medications of long duration and influence on both physical and mental development, we should also aim to increase dialogue between the medical specialities treating children and their families.

### **Limitations**

The data evaluated in this study were originally collected for clinical purposes at a time when there were no systematic SGA follow-up procedures available in clinical work. The results need to be interpreted with caution and more systematic research of SGA follow-up practices is needed in the future.

### **Ethical approval**

The study was approved by the ethics committee of the Pirkanmaa Hospital District. All data were originally collected for clinical purposes. The patients and their families were not contacted and their treatment was not affected in any way by the study; hence, no informed consent was required.

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### **Conflicts of interest**

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